**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Before the Board of Patent Appeals and Interferences**

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| In re Appeal regarding Patent Application of | | |
| Applicants : | GOELET, Philip *et al.* | Examiner: MYERS, Carla J. |
| Application No.: | 09/258,132 | Art Unit: 1634 |
| Filing Date: | 26 February 1999 | |
| Title: | Nucleic Acid Typing By Polymerase Extension of Oligonucleotides Using Terminator Mixtures | |

Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, New York 10022

18 November 2008

Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

# REPLY BRIEF

Rebuttal

In the Office Action of 22 May 2007 on appeal, pending claims 64 and 66 through 71 inclusive of the subject patent application were finally rejected under 35 U.S.C. § 103(a) as unpatentable over European published patent application EP 0 412 883 A1 to Cohen *et al.* ("the Cohen *et al.* '883 published European application") or French patent 2,650,840 also to Cohen *et al.* ("the Cohen *et al.* '840 French patent"), each in view of international PCT published patent application WO 90/11372 to Davis *et al.* ("the Davis *et al.* '372 PCT published application"), and, in the case of claim 68, further in view of United States patent No. 5,332,666 to Prober *et al.* ("the Prober *et al.* '666 patent"), or, in the case of claim 71, further in view of United States patent No. 4,962,020 to Tabor *et al.* ("the Tabor *et al.* '020 patent"). (For the reasons explained in the Appeal Brief of 26 June 2008, only the English translation of the Cohen *et al.* '840 French patent of record in the subject application will be referred to below.)

Regarding the hypothetical combination of the process for identifying a single base in a nucleic acid sequence of the Cohen *et al.* '840 French patent with the method of the Davis *et al.* '372 PCT published application for testing a single sample of DNA at multiple loci proposed in the final rejections on appeal, the attorneys for the appellants have contended that the Cohen *et al.* patent taught directly away from the combination. In appellants' Appeal Brief of 26 June 2008, for example, it was noted that the Cohen *et al.* '840 French patent at page 6, lines 29 through 33 disclosed that a purported advantage of the process of the patent was that the process did not require immobilization of the nucleic acid on a membrane. The full quote – a single, one-sentence paragraph – is as follows:

> One specific advantage of the process pursuant to the invention is that it defines the operative conditions independently of the nucleotide base to be identified, and <u>does not require immobilization of the nucleic acid on a membrane</u>. [Underlining added.]

Significantly, the quoted one-sentence paragraph makes no reference to any specific previously known technique for identifying a mutation in a nucleic acid sequence. Moreover, the quoted sentence characterizing as an advantage of the process of the Cohen *et al.* patent the lack of a

requirement to immobilize the nucleic acid on a membrane was part of a detailed description of the process of the patent in the patent specification and was not part of a "background-art" introductory section of the specification where specific prior art was described and distinguishing features of such specific prior art pointed out. It is submitted that the quoted sentence thus constituted a broad, unqualified teaching in the Cohen *et al.* '840 French patent away from any technique which required immobilization of nucleic acid on a membrane.

Consistent with the unqualified teaching away from any technique which required immobilization of nucleic acid on a membrane in a detailed description of the process of the Cohen *et al.* '840 French patent in the patent specification noted in the preceding paragraph, the introductory section of the specification of the Cohen *et al.* patent expressly distinguished the method of the patent, at least in part on the basis of membrane-immobilization requirements, from three different techniques previously known for identifying a mutation in nucleic acid involving a single nucleotide position. The three previously known techniques distinguished from the method of the Cohen *et al.* patent were identified in the patent specification as (1) a long-probe technique, (2) a short-probe technique, and (3) the method of United States patent 4,656,127 to Mundy ("the Mundy '127 patent"). The three previously known techniques differed fundamentally one from another in the manner in which the single nucleotide mutation was identified, but had in common, in embodiments to which relevant distinguishing comments in the Cohen *et al.* patent applied, steps involving immobilizing nucleic acid on a membrane and detecting oligonucleotide probes bearing labels hybridized along at least a portion of their length to the nucleic acid immobilized on the membrane. As discussed in detail below, in distinguishing the three previously known techniques, the Cohen *et al.* French patent taught that each technique was disadvantageous relative to the analysis method of the patent at least in part because, as ordinarily practiced, each of the previously known techniques involved immobilization of nucleic acid on a membrane. Because of the fundamental differences in the manner in which the single nucleotide mutation was identified in the three techniques, the characterization in the introductory section of the specification of the Cohen *et al.* '840 French patent of the common requirement to immobilize nucleic acid on a membrane as a disadvantage

of the three different techniques relative to the method of the Cohen *et al.* patent which had no such immobilization requirement supported and reinforced – while not restricting in any way – the broad, unqualified teaching in the detailed description of the Cohen *et al.* patent away from any technique which required immobilization of nucleic acid on a membrane noted in the preceding paragraph.

At page 4, lines 22 through 24 of the Cohen *et al.* '840 French patent, immobilization of DNA was characterized unfavorably as a "complex operational protocol," which provided a clear technical basis in support of the unqualified teaching in the Cohen *et al.* patent away from any technique which required immobilization of nucleic acid on a membrane. Persons of ordinary skill in the art would have appreciated that a typical protocol for immobilizing nucleic acid on a membrane would have involved obtaining a membrane of a suitable material, transferring the nucleic acid in solution to the surface of the membrane by spotting or by a Southern-blot transfer from an electrophoresis gel, and baking the membrane bearing the nucleic acid in a vacuum oven at 80□ for a specified time. The Cohen *et al.* '840 French patent plainly taught at page 4, lines 22 through 24 and page 6, lines 29 through 33 that such complex operational protocol required to immobilize nucleic acid on a membrane was disadvantageous in and of itself in any process for identifying a single base in a nucleic acid sequence and thus to be avoided.

In addition to noting that any requirement to immobilize nucleic acid on a membrane was a disadvantage to be avoided, the Cohen *et al.* '840 French patent taught that attempting to hybridize a nucleic-acid probe with specificity to complementary nucleic acid which had been immobilized on a membrane was fraught with difficulty. As explained in the Appeal Brief of 26 June 2008, two paragraphs of the Cohen *et al.* patent at page 2, line 19 through page 3, line 17 read in their entirety taught that the long-probe technique and the short-probe technique for identifying a single base in a nucleic acid sequence, both of which techniques involved hybridizing a probe with specificity to complementary nucleic acid immobilized on a membrane, shared a disadvantage in addition to the disadvantage of requiring nucleic acid to be immobilized on a membrane; namely, the disadvantage that "the temperature conditions are difficult to master

to achieve suitable hybridization." It is submitted therefore that Cohen *et al.* '840 French patent taught away from attempting to hybridize a nucleic-acid probe to complementary nucleic acid immobilized on a membrane because, according to the patent, the temperature conditions were difficult to master.

The method of the Davis *et al.* '372 PCT published application for testing a single sample of DNA simultaneously at multiple loci which was proposed in the Office Action on appeal as obvious to combine with the analysis method of the Cohen *et al.* '840 French patent involved immobilization of nucleic acid on a membrane, which the Cohen *et al.* patent taught unqualifiedly was a disadvantage. In addition, the method of the Davis *et al.* published application required hybridizing a nucleic acid "tail" with high specificity to exactly complementary nucleic acid immobilized on a membrane in the presence of other noncomplementary nucleic acid immobilized on the membrane, which the Cohen *et al.* patent would have suggested was problematic in view of the teachings of the patent that temperature conditions were difficult to master to achieve suitable hybridization when attempting to hybridize nucleic acid with specificity to complementary nucleic acid immobilized on a membrane. The attorneys for the appellants have contended, therefore, that the hypothetical combination proposed in the Office Action on appeal would have been understood by persons of ordinary skill in the art as of the effective filing date of the subject application as running directly counter to the teachings of the Cohen *et al.* patent. In *KSR International* v. *Teleflex* 550 US 398; 127 S. Ct 1727, 1740; No. 04-1350, slip op. 12 (U.S. April 30, 2007), the United States Supreme Court has affirmed the "principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." Thus in the Appeal Brief of 26 June 2008, it was contended that persons of ordinary skill in the art would not have deemed it obvious to combine the process of the Cohen *et al.* '840 French patent with the method of the Davis *et al.* '372 PCT published application as proposed in the Office Action of 22 May 2007 on appeal and that the rejections of the Office Action under 35 U.S.C. § 103(a) were therefore unjustified and should be reversed.

Turning now to the Examiner's Answer of 18 September 2008, it is submitted that the Examiner's Answer failed to take proper account of the broad, unqualified teaching in the Cohen *et al.* '840 French patent away from any technique which required immobilization of nucleic acid on a membrane discussed above, of which the method of the Davis *et al.* '372 PCT published application would have been recognized to be an example.

Generally speaking, it was conceded in the Examiner's Answer that the Cohen *et al.* '840 French patent taught away from certain previously known techniques such as the short-probe allele-specific hybridization technique (unduly narrowly defined, it is submitted), but the Examiner's Answer did not accord a fair reading to the broad, unqualified teaching in the Cohen *et al.* '840 French patent at page 6, lines 29 through 33 cited in the Appeal Brief away from any technique for identifying a mutation in nucleic acid involving a single nucleotide position which required immobilization of nucleic acid on a membrane, which unqualified teaching away did not reference any specific previously known technique for identifying a mutation in nucleic acid, as discussed above.

In addition, it is submitted that the Examiner's Answer failed to take proper account of more specific teachings in the Cohen *et al.* '840 French patent away from particular, identified previously-known techniques which involved immobilization of nucleic acid on a membrane such as temperature conditions being difficult to master to achieve suitable hybridization in the case of the long probe and short probe techniques and the use of a marked probe in the case of the method of the Mundy '127 patent which, it is submitted, persons of ordinary skill in the art would have recognized applied by direct analogy to the method of the Davis *et al.* published application.

It is submitted that the failure in the Examiner's Answer and in the Office Action on appeal to take proper account of teachings in the Cohen *et al.* '840 French patent away from techniques which required immobilization of nucleic acid on a membrane and hybridization of complementary nucleic acid to such immobilized nucleic acid in connection with the

hypothetical combination of the process for identifying a single base in a nucleic acid sequence of the Cohen *et al.* patent with the method of the Davis *et al.* published application for testing a single sample of DNA at multiple loci proposed in the final rejections on appeal constitutes reversible error.

For conciseness, it will not be attempted to address each and every point in the Examiner's Answer of 18 September 2008 in the present rebuttal, particularly since many of the positions taken in the Examiner's Answer were essentially repeated from the final Office Action of 22 May 2007 on appeal and have been fully discussed in the Appeal Brief of 26 June 2008.

Turning now to specific arguments in the Examiner's Answer, in the paragraph bridging pages 9 and 10 of the Examiner's Answer, it is argued that:

> [a]t page 2, lines 10-17, Cohen addresses the effect of temperature on the specificity of hybridization using probes to "detect a mutation involving a single base." These teachings are not considered to be relevant to the method of Davis because the method of Davis does not require the use of a probe to directly hybridize to and detect a single base mutation in a target nucleic acid. Rather, the method of Davis involves only performing the step of hybridizing primer tails that are fully complementary to the primer tails (i.e., hybridization is not with a target nucleic acid comprising a single base mutation).

It is correct that it is pointed out in the Cohen *et al.* patent at page 2, lines 4 through 7 that hybridization as a diagnostic tool can be limited by a lack of specificity and at page 2, lines 8 through 18 that the temperature is a particularly critical variable with respect to hybridization. However, it is not correct as implied in the quotation from the Examiner's Answer set out above that the probes described in the paragraph bridging pages 2 and 3 of the Cohen *et al.* patent beginning "[t]hus, to detect a mutation involving a single base," necessarily hybridize directly to a single base mutation in a target nucleic acid, as discussed in the following paragraph.

The paragraph in question bridging pages 2 and 3 of the Cohen *et al.* patent begins:

> Thus, to detect a mutation involving a single base, depending on the case generally two types of probes can be used: nucleic acid probes called long probes, generally over 150 nucleotides, or nucleic acid probes called short probes, generally between 17 and 24 nucleotides.

As explained in the paragraph in question at page 2, lines 24 through 33, long probes could be used in a "Southern blot" restriction-analysis technique when a single-base mutation occurred at a site recognized by a restriction enzyme. As persons of ordinary skill in the art would have recognized, it was treatment of the nucleic acid to be analyzed with the restriction enzyme causing either restriction or no restriction depending on the presence of the single base mutation in the nucleic acid which resulted in the detection of the mutation. See the detailed discussion of the long probe Southern blot restriction-analysis technique in the Appeal Brief of 26 June 2008 at page 16, line 24 through page 19, line 9. A long probe bearing a label was used to visualize the size of the nucleic acid after treatment of the nucleic acid with the restriction enzyme, size fractionation of the resulting nucleic-acid fragments by electrophoresis on a gel, transfer of the nucleic-acid fragments from the gel to a membrane by the Southern blot transfer technique, and immobilization of the nucleic-acid fragments on the membrane. Importantly, such long probes referred to in the Cohen *et al.* patent would have been synthesized to hybridize to a stretch of the nucleic acid being analyzed displaced from the site of the potential mutation and exactly complementary to the long probe. See, for example, lines 12 through 15 of page 169 of the textbook *Biochemistry*, third edition, by L. Stryer of record in the subject application and included in the evidence appendix accompanying the Appeal Brief of 26 June 2008. Nonetheless, as discussed below, the Cohen *et al.* '840 French patent unambiguously taught that temperature conditions were difficult to master to achieve suitable hybridization in the long-probe Southern blot restriction-analysis technique, which required hybridization of the long probe to exactly complementary nucleic acid immobilized on a membrane.

In contrast to the long-probe technique, the short-probe technique described generally passim from page 2, line 19 to page 3, line 17 the Cohen *et al.* '840 French patent involved a short probe (generally between 17 and 24 nucleotides according to the Cohen *et al.* patent) which would have been synthesized to span the site of potential mutation in the nucleic acid to be analyzed and to be complementary to the nucleic acid with the possible exception of the position of the potential single-base mutation. According to page 3, lines 3 through 9 of the Cohen *et al.* patent, hybridization and rinsing conditions were selected in the short-probe technique so that

hybridization of the probe would be achieved only in the case of perfect complementarity. The short-probe technique described in the paragraph bridging pages 2 and 3 of the Cohen *et al.* '840 French patent would thus have been recognized by persons of ordinary skill in the art to be an allele-specific hybridization technique.

Lines 10 through 17 of page 3 of the Cohen *et al.* '840 French patent, a separate paragraph which immediately follows the single paragraph concerning the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique bridging pages 2 and 3 of the Cohen *et al.* patent, identified two particular disadvantages which, it is submitted, a fair reading of the paragraph bridging pages 2 and 3 and the paragraph of lines 10 through 17 of page 3 of the patent would have shown to have applied both to the long-probe technique and to the short-probe technique, as discussed in the following paragraphs. In this regard, it is submitted that the reading of the paragraph of lines 10 through 17 of page 3 of the Cohen *et al.* patent in the Examiner's Answer at page 10, line 18 through page 11, line 21 as applying solely to the short-probe allele-specific hybridization technique to the exclusion of the long-probe Southern-blot restriction-analysis technique is incorrect as a matter of straightforward textual interpretation. It should be noted that the quotation from the paragraph concerning the long-probe technique and the short-probe technique bridging pages 2 and 3 of the Cohen *et al.* patent and the following paragraph identifying disadvantages set out in the Examiner's Answer at page 10, line 23 through page 11, line 7 is fundamentally misleading, since the discussion in the paragraph bridging pages 2 and 3 concerning the long-probe Southern-blot restriction-analysis technique is simply omitted without discussion or justification and the textually significant paragraph break between the paragraph bridging pages 2 and 3 of the Cohen *et al.* patent and the paragraph at page 3, lines 10 through 17 identifying disadvantages is likewise simply omitted without discussion or justification. The discussion of the characterization the long-probe technique by the Cohen *et al.* patent in the Examiner's Answer at page 18, line 22 through page 11, line 21 is similarly incomplete and the conclusions similarly incorrect, as the following discussion demonstrates.

The paragraph identifying disadvantages at page 3, lines 10 through 17 of the Cohen *et al.* '840 French patent immediately following the paragraph concerning the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique bridging pages 2 and 3 of the Cohen *et al.* patent is discussed in the following paragraphs. For convenience, we begin by quoting the paragraph under discussion:

> However, these various methods all have a certain number of disadvantages:
>
> – the temperature conditions are difficult to master to achieve suitable hybridization;
>
> – the mandatory presence of a restriction site may be required;
>
> – the nucleic acid is immobilized on a membrane (Southern blot). [Underlining added.]

In the paragraph just quoted, the Cohen *et al.* '840 French patent identified three separate disadvantages, but did not in express terms identify to which method or methods the various disadvantages were intended to apply. However, as a matter of straightforward textual interpretation, the content of the paragraph and the context of the paragraph would have made clear to a person of ordinary skill in the art the methods to which the three disadvantages were intended to apply.

First, regarding the context of the paragraph quoted above, it would have been noted that that paragraph immediately followed as a separate paragraph the single paragraph bridging pages 2 and 3 of the Cohen *et al.* patent which introduced and described the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique, the first sentence of which paragraph referred to both long probes and short probes. Second, regarding both the content and the context of the paragraph quoted above, it would have been noted that the three disadvantages identified in the paragraph immediately following the paragraph introducing and describing the long-probe technique and the short-probe technique were introduced with the following language: "these various methods all have a certain number of disadvantages." [Underlining added.] It is submitted that the language "these various methods all" in the opening clause of the paragraph immediately following the paragraph introducing and describing the

long-probe technique and the short-probe technique would have been understood as referring to all the various methods described in the preceding text; namely, the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique. The terms "all" and "various" and "methods" in the plural form would have been altogether misdescriptive had it been intended to refer in the quoted paragraph to only the one short-probe technique described in the paragraph immediately preceding the quoted paragraph to the exclusion of the long-probe technique also described in that preceding paragraph as contended in the Examiner's Answer. For the reasons set forth above, it is submitted that a person of ordinary skill in the art would have understood the language "these various methods all have a certain number of disadvantages" at the opening of the paragraph at page 3, lines 10 through 17 of the Cohen *et al.* '840 French patent quoted above to refer to both the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique described in the paragraph bridging pages 2 and 3 of the patent which immediately preceded the quoted paragraph.

Turning next to the language in the paragraph at page 3, lines 10 through 17 of the Cohen *et al.* '840 French patent setting forth the three disadvantages, the first and third disadvantages were stated in unconditional terms; the second disadvantage was stated as a possibility; i.e. "a restriction site *may* be required." [Emphasis added.] In the paragraph bridging pages 2 and 3 of the Cohen *et al.* '840 French patent, it was noted that the process involving hybridization by means of a long probe required that the mutation involve a restriction site, and that, if that were not the case, a process involving hybridization by means of a short probe could be used. Consequently, the second disadvantage quoted above stating that "the mandatory presence of a restriction site may be required" would have been understood as applying to the long-probe Southern-blot technique, but not to the short-probe Southern-blot technique as described.

Since, as demonstrated above, the introductory language "these various methods all have a certain number of disadvantages" at the beginning of the paragraph at page 3, lines 10 through 17 of the Cohen *et al.* '840 French patent quoted above would have been understood to refer to

both the long-probe Southern-blot restriction-analysis technique and the short-probe allele-specific hybridization technique, and since the first and third disadvantages identified in the quoted paragraph were stated in unconditional terms, the first and third disadvantages would have been understood by persons of ordinary skill in the art as applying both to the long-probe Southern-blot restriction analysis technique and to the short-probe allele-specific hybridization technique described in the paragraph bridging pages 2 and 3 of the Cohen *et al.* patent. Thus it is submitted that the Cohen *et al.* '840 French patent taught that the long-probe Southern-blot restriction-analysis technique shared with the short-probe allele-specific hybridization technique a pair of disadvantages; namely, "the temperature conditions are difficult to master to achieve suitable hybridization" and "the nucleic acid is immobilized on a membrane (Southern blot)." Moreover, it is submitted that persons of ordinary skill in the art would have understood from the Cohen *et al.* '840 French patent that the long-probe technique had the disadvantage of: "the temperature conditions are difficult to master to achieve suitable hybridization;" notwithstanding the recognition of such persons, as noted above that the probe of the long-probe Southern-blot restriction-analysis technique was used to visualize an electrophoresis pattern from nucleic acid digested by a restriction enzyme in solution and thereafter immobilized on a membrane by hybridizing to a stretch of the immobilized nucleic acid displaced from the site of the potential mutation and exactly complementary to the long probe. Persons of ordinary skill in the art would have recognized from the fact that hybridization with an oligonucleotide probe was used to visualize an electrophoretic pattern of nucleic acid fragments immobilized on a membrane in the long-probe Southern-blot restriction-analysis technique that specificity of the hybridization was an important consideration in the technique. Page 2, lines 4 through 18 of the Cohen *et al.* '840 French patent implied that temperature was a critical parameter with respect to specificity of hybridization.

The disadvantage discussed above of temperature conditions being difficult to master to achieve suitable hybridization identified by the Cohen *et al.* '840 French patent for hybridizing an over 150-nucleotide-long long probe to an exactly complementary stretch of nucleic acid immobilized on a membrane in accordance with the long-probe Southern-blot restriction-analysis

technique would, it is submitted, have been recognized by persons of ordinary skill in the art to apply essentially equally to the method of the Davis *et al.* '372 PCT publication. The method of the Davis *et al.* publication involved irreversibly binding respectively different tail-complementary oligonucleotides to a membrane or other substrate at specific locations corresponding to the respective tail sequences of a set of tail-bearing extension primers and applying putative extension products to the substrate under conditions permitting hybridization of the tails of the extension products to respective oligonucleotides complementary to the tails bound to the substrate at specific locations for identifying each location having extension product which bore a label hybridized to the tail-complementary oligonucleotide at the specific location and so identifying a particular single-nucleotide-polymorphism allele corresponding to the location. As indicated in the Examiner's Answer at page 11, lines 15 through 21, the method of the Davis *et al.* '372 PCT publication did not require hybridization specificity sufficient to detect the presence of a single nucleotide variation between a target nucleic acid and a probe. However, the long-probe Southern-blot restriction-analysis technique likewise did not require such hybridization specificity, yet the Cohen *et al.* '840 French patent taught that in the long-probe Southern-blot technique, "the temperature conditions are difficult to master to achieve suitable hybridization," which the Cohen *et al.* patent expressly characterized as a disadvantage of the technique. Persons of ordinary skill in the art with the Cohen *et al.* patent and the Davis *et al.* publication at hand would have recognized that, in the method of the Davis *et al.* publication, the temperature conditions would have been difficult to master to achieve suitable hybridization just as in the long-probe Southern-blot restriction-analysis technique, which would have been a disadvantage leading away from the hypothetical combination of the process of the Cohen *et al.* '840 French patent with the method of the Davis *et al.* publication proposed by the examiner in the Office Action on appeal.

Furthermore, the disadvantage of temperature conditions being difficult to master to achieve suitable hybridization which the Cohen *et al.* '840 French patent taught was suffered by the short-probe allele-specific hybridization technique would, it is submitted, have been recognized by persons of ordinary skill in the art to apply by analogy to the method of the Davis

*et al.* '372 PCT publication essentially as it applied to the short-probe technique. It was conceded in the Examiner's Answer that the Cohen *et al.* patent taught that the temperature conditions were difficult to master to achieve suitable hybridization in connection with the short-probe allele-specific hybridization technique. See, for example, page 11, lines 8 through 18 and page 19, lines 12 through 18 of the Examiner's Answer. As noted above, the Cohen *et al.* patent disclosed at page 2, lines 22 through 24 that the probes of the short-probe technique were generally between 17 and 24 nucleotides in length. Such probes between 17 and 24 nucleotides in length were hybridized in the short-probe technique to nucleic acid to be analyzed which had been immobilized on a membrane, as was evident from the third disadvantage attributed to the short-probe technique (as well as to the long-probe technique) by that the Cohen *et al.* patent at page 3, lines 16 and 17. As noted above, in the method of the Davis *et al.* '372 PCT publication for testing a single sample of DNA simultaneously at multiple loci, the presence of a particular allele at a particular locus would have been detected by detecting the presence of a labeled probe/extension product at a particular location on a membrane determined by hybridization of a unique "tail" sequence of nucleotides attached to the probe/extension product to nucleic acid complementary to the tail immobilized at that location on the membrane. According to page 21, line 27 through page 22, line 1 of the Davis *et al.* publication, such tail sequences were preferably only 14 nucleotides long – significantly shorter than the short probes between 17 and 24 nucleotides in length of the short-probe allele-specific hybridization technique. Moreover, according to page 23, lines 19 through page 24, line 1 of the Davis *et al.* publication, two different 14-nucleotide-long tail sequences in the method of the publication could have differed by only a single nucleotide, although a difference of at least two nucleotides was stated to be preferred. The specificity of the hybridization of a tail sequence to the precise complementary sequence immobilized at a particular location on the membrane – and only that sequence in the presence of other, closely similar sequences immobilized at other locations on the membrane – would have been critical to the accuracy of the method of the Davis *et al.* '372 PCT publication, as, it is submitted, a person of ordinary skill in the art would have recognized. The assertion in the Examiner's Answer at page 23, lines 4 through 13 that there was no requirement in the method of the Davis *et al.* publication for a primer tail to distinguish by hybridization between

fully complementary nucleic acids and nucleic acids which differed at a single point is misleading, since the method of the Davis *et al.* publication does require primer tails shorter than the short probes of the short-probe technique to distinguish by hybridization among various closely similar nucleotide sequences (including sequences which could differ by only a single nucleotide) immobilized at various locations on a membrane. It is submitted that a person of ordinary skill in the art with the Cohen *et al.* '840 French patent and the Davis *et al.* '372 PCT publication at hand would have concluded that, since the tail sequences of the probe/extension products of the method of the Davis *et al.* publication were even shorter than the short probes of the short-probe allele-specific hybridization technique described in the Cohen *et al.* patent and since the method of the Davis *et al.* publication would have shared with the short-probe technique a requirement for high-specificity hybridization of short sequences of nucleotides to nucleic acid immobilized on a membrane, the method of the Davis *et al.* publication would have suffered the disadvantage of temperature conditions being difficult to master to achieve suitable hybridization which the Cohen *et al.* patent taught was a disadvantage of the short-probe allele-specific hybridization technique. It is submitted therefore that by virtue of the teaching in the Cohen *et al.* '840 French patent that the short-probe allele-specific hybridization technique suffered the disadvantage of temperature conditions being difficult to master to achieve suitable hybridization, the Cohen *et al.* patent taught away from the hypothetical combination of the process of the Cohen *et al.* '840 French patent with the method of the Davis *et al.* '372 PCT publication proposed by the examiner in the Office Action on appeal.

Turning now to distinctions drawn in the Cohen *et al.* '840 French patent between the process for identifying a single base in a nucleic acid sequence of the Cohen *et al.* patent and the method of the Mundy '127 patent for detecting mutations in DNA and RNA, certain drawbacks in the method of the Mundy patent pointed out in the Cohen *et al.* patent would have been recognized by persons of ordinary skill in the art to apply by close analogy to the method of the Davis *et al.* '372 PCT publication. The identification in the Cohen *et al.* patent of such drawbacks in the method of the Mundy patent thus would have amounted to a teaching away

from the hypothetical combination of the process of the Cohen *et al.* patent with the method of the Davis *et al.* publication proposed in the Office Action on appeal.

The method of the Mundy '127 patent called for irreversibly binding single-stranded chains of a target nucleic acid to a nitrocellulose filter. The method of the patent further called for hybridizing a labeled probe to the target nucleic acid chain to form a hybrid in which one end of the probe would have been positioned adjacent to the specific base to be identified. Regarding the labeled probe, it was disclosed at column 5, lines 36 through 38 of the Mundy '127 patent that the probe could have two sequences, one to hybridize to the target chain and one to carry the label. After the hybrid complex of labeled probe and target nucleic acid chain would have been formed, a digestion-resistant nucleotide derivative such as a thionucleotide would have been added under conditions to cause it to join the end of the probe if it were complementary to the specific base. The resulting hybrid complex would have then been treated with an exonuclease enzyme under conditions such that, if present on the end of the probe, the digestion-resistant nucleotide derivative would have protected the probe from digestion. Observation of the presence or absence of the probe label attached to the target nucleic-acid chain after the digestion step would have detected the mutation of specific base in the target chain. See the Appeal Brief of 26 June 2008 at page 24, line 21 through page 26, line 7 for a more detailed description of the method of the Mundy '127 patent.

Regarding the method of the Mundy '127 patent, the Cohen *et al.* '840 French patent stated at page 4, lines 14 through 17 that

> For its implementation [the method of the Mundy patent] requires immobilization of the nucleic acid on a membrane, and also marking (of the probe or of the nucleotide derivative).

Thus in connection with distinguishing the method of the Mundy '127 patent, the Cohen *et al.* patent taught once again that immobilization of nucleic acid on a membrane was a disadvantage in a method for detecting a single-base mutation. The teaching away from a requirement to immobilize nucleic acid on a membrane in the context of distinguishing the method of the Mundy patent was particularly significant with regard to by analogy teaching

away from the method of the Davis *et al.* '372 PCT publication, since the Mundy patent disclosed a "spotting" technique for accomplishing the membrane immobilization which was different from the Southern-blot transfer employed in the long-probe Southern-blot restriction-analysis technique discussed above and was closely similar to the immobilization technique disclosed in the Davis *et al.* publication. Compare, for example, column 5, lines 6 through 11 of the Mundy '127 patent with page 6, lines 7 through 22 and page 21, lines 8 through 12 of the Davis *et al.* '372 PCT publication.

In the Examiner's Answer at page 10, lines 7 through 15, in an effort to avoid application of the teaching in the Cohen *et al.* patent that immobilization of nucleic acid on a membrane was a disadvantage in the method of the Mundy '127 patent to characterize the membrane immobilization of nucleic acid in the method of the Davis *et al.* '372 PCT publication as likewise a disadvantage, it was pointed out that the nucleic acid immobilized on a membrane was a target nucleic acid, in asserted contrast to capture-probe nucleic acid immobilized on a membrane in the method of the Davis *et al.* publication. It is submitted that persons of ordinary skill in the art would have regarded the asserted distinction between target nucleic acid immobilized on a membrane and capture-probe nucleic acid immobilized on a membrane as a "distinction without a difference." It was recognized in both the Cohen *et al.* patent (at page 8, lines 11 and 12) and in the Davis *et al.* publication (at page 2, lines 1 through 5) that target nucleic acid to be analyzed for a mutation could be amplified by conventional amplification methodology, thereby eliminating any distinction between target nucleic acid and capture-probe nucleic acid in terms of quantity of material to be immobilized on the membrane, although it was noted in the Davis *et al.* publication at page 2, lines 11 and 12 polymerase chain reaction (PCR) amplification techniques could give rise to false signals arising from contamination. Moreover, as pointed out in the preceding paragraph, the Mundy patent and the Davis *et al.* publication disclosed similar "spotting" techniques as suitable for accomplishing the immobilization of nucleic acid on a membrane for their respective analysis methods, notwithstanding differences in the source of the nucleic acid to be immobilized. If the spotting technique for immobilization on a membrane of

one of the methods constituted a "complex operational protocol" to be avoided (see page 4, lines 22 through 25 of the Cohen *et al.* patent), so would the spotting technique of the other method.

For the reasons set forth above, it is submitted that a person of ordinary skill in the art would have recognized that the plain teaching in the Cohen *et al.* patent that immobilization of the target nucleic acid on a membrane was a disadvantage with regard to the method of the Mundy '127 patent implied by close analogy that immobilization of the tail-complement nucleic acid on a membrane was a disadvantage with regard to the method of the Davis *et al.* '372 PCT publication. The teaching in the Cohen *et al.* patent that immobilization of the target nucleic acid on a membrane was a disadvantage in the method of the Mundy '127 patent thus would have been understood to have constituted a teaching away from the hypothetical combination of the process of the Cohen *et al.* patent with the method of the Davis *et al.* publication proposed in the Office Action on appeal.

In the quotation above regarding the method of the Mundy '127 patent, the Cohen *et al.* '840 French patent identified a second disadvantage of the method of the Mundy patent independent of the disadvantage of the requirement to immobilize nucleic acid on a membrane; namely, a requirement for marking the probe. In the Examiner's Answer at page 10, lines 9 through 12 it was asserted that the teaching of the Cohen *et al.* patent away from the method of the Mundy patent on the basis of the requirement for marking the probe would not have constituted a teaching away from the method of the Davis *et al.* '372 PCT publication because the method of the Davis *et al.* publication did not require contacting immobilized nucleic acid with a "'marked' (i.e., labeled) probe." However, the various different probes of the method of the Davis *et al.* '372 PCT publication included unique tail sequences which served to identify the probes, so that the probes could well have been regarded by a person of ordinary skill in the art as labeled probes, or at least closely analogous to labeled probes. It would seem that the procedure set out at page 49, line 3 through page 50, line 17 of the Davis *et al.* publication would have constituted an "operational protocol" of at least comparable complexity to an operational protocol to apply a conventional label to a probe. Moreover, regarding the specific marked

probes of the method of the Mundy '127 patent which the Cohen *et al.* patent identified as constituting a disadvantage, the Mundy patent disclosed at column 5, lines 36 through 38 that the probe could have two sequences, one to hybridize to the target chain and one to carry the label, which would have been closely analogous to the probes with tail sequences of the method of the Davis *et al.* publication. It is submitted, therefore, that a person of ordinary skill in the art would have recognized that the teaching in the Cohen *et al.* patent that marking of the probe was a disadvantage with regard to the method of the Mundy '127 patent implied by analogy that applying unique identifying tail sequences to probes in the method of the Davis *et al.* '372 PCT publication was a disadvantage. The teaching in the Cohen *et al.* '840 French patent that marking of the probe was a disadvantage in the method of the Mundy patent thus would have amounted to a teaching away from the hypothetical combination of the process of the Cohen *et al.* patent with the method of the Davis *et al.* publication proposed in the Office Action on appeal.

In the Examiner's Answer at page 24, lines 12 through 19, *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) was cited for the proposition that for a finding of obviousness, all that is required is a reasonable expectation of "success." However, in the *O'Farrell* case, the prior art reference contained an express suggestion of the purported invention, although there was no indication that the suggestion had actually been tried. The "success" in the "reasonable expectation of success" standard of obviousness refers to successfully carrying out an express suggestion of a purported invention found in the prior art. There does not appear to have been any express teaching in the prior art away from the suggested invention in the *O'Farrell* case. Had there been teaching in the prior art away from the suggested invention, the "principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious" of the *KSR International* case cited above would have come into play. The final rejections under 35 U.S.C. § 103(a) on appeal in the instant case differ from the facts of the *O'Farrell* case in two crucial respects. First, neither the Cohen *et al.* '840 French patent nor the Davis *et al.* '372 PCT publication nor any other art of record suggests the hypothetical combination of the process of the Cohen *et al.*

patent with the method of the Davis *et al.* publication proposed in the Office Action on appeal. Consequently, there is no prior-art suggestion of the hypothetical combination to which to apply the "reasonable expectation of success" standard of the *O'Farrell* case. Second, the Cohen *et al.* '840 French patent contains multiple, independent teachings away from the hypothetical combination, as discussed at length above and in the Appeal Brief of 26 June 2008. Such teachings away from the hypothetical combination constitute strong hypothetical evidence of the nonobviousness of the claimed invention under the principle of the *KSR International* case noted above.

Even further from the final rejections under 35 U.S.C. § 103(a) on appeal in the instant case than the facts of the *O'Farrell* case are the facts of *In re Gurley*, 27 F.3d 551, 554 (Fed. Cir. 1994) cited on page 13 of the Examiner's Answer. In the *Gurley* case, a prior-art reference disclosed that certain claimed printed circuit material had actually been produced, although it was characterized as inferior in certain respects to other printed circuit material. In the instant case, the hypothetical combination of the process of the Cohen *et al.* patent with the method of the Davis *et al.* publication proposed in the Office Action on appeal is merely a hypothetical combination. The principles of the *Gurley* case are therefore not applicable to the hypothetical combination proposed in the Office Action on appeal.

Conclusion

For the reasons set forth above and in the Appeal Brief of 26 June 2008, it is submitted that the claims of the subject application are patentable over the art of record considered alone or in any combination. Reversal of the final rejections and allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Appellants

by: _____
J. David Ellett, Jr.
(Reg. No. 27,875)

Telephone No. (212) 813-1600